Document #: 445562
230p81512

GBP81512
9927106.6

Cancer Treatment

The present invention relates to the treatment of cancers.

BACKGROUND OF THE INVENTION

US Patent 5,089,273 relates to compounds identified as ecteinascidins. In particular, it relates to ecteinascidins 729, 743, 759A, 759B and 770. The compounds are disclosed to have antibacterial properties and some are also useful as antitumor agents.

SUMMARY OF INVENTION

We have found that the ecteinascidins, in particular ecteinascidin 743, are suited for treatment of sarcomas, notably soft tissue sarcomas. Sarcomas which may be considered for treatment include osteosarcoma, liposarcoma and fibrosarcoma.

The ecteinascidins appear to have suitability for treatment of refractory advanced sarcomas, and thus in a special aspect the invention provides a method of treating a treated patient who has proved refractory to other treatment. More notably, the method seems applicable to patients treated with chemotherapy, such as anthracycline and/or alkylators.

In a preferred aspect, the present invention involves identifying patients who have been treated for cancer, and treating them with an ecteinascidin.

Pharmaceutical formulations are also provided, as well methods of treatment using the ecteinascidin or using the compositions, as well as methods for preparing pharmaceutical compositions for use in the method of treatment.

The ecteinascidins in the form of ecteinascidin 743 seem suited for treatments in view of the relationship of the dose-limiting toxicity to pharmacokinetics.

PREFERRED EMBODIMENTS

The ecteinascidins as typified by ecteinascidin 743 have exceptional activity in the treatment of sarcomas, mesotheliomas, cartilage tumours and other cancers. Examples of human sarcomas to be treated include osteosarcomas and soft tissue sarcomas, leiomyosarcomas, fibrosarcomas and mesotheliomas.

Examples of pharmaceutical compositions of this invention include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compounds or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the composition of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. Intravenous delivery may be carried out over any suitable time period. We prefer that infusion times for the ecteinascidin of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Indeed, a typical time is about 3 hours. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks.

Pharmaceutical compositions containing ecteinascidins may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the ecteinascidin will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated.

Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compositions of this invention may be used with other drugs. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carboplatin, oxaliplatin , paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics; and

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine.

We have found that the potency of ecteinascidin 743 is enhanced by combination therapy with dexamethasone. The finding was not predictable.

According to the present invention, and based on this finding, we provide new ecteinascidin combinations for therapy of mammalian cancers, including:

combinations of ecteinascidins, notably ecteinascidin 743, with steroid analogues, in particular dexamethasone;

combinations of ecteinascidins, notably ecteinascidin 743, with anti-inflammatory drugs, in particular dexamethasone; and

combinations of ecteinascidins, notably ecteinascidin 743, with anti-emetic drugs, in particular dexamethasone.

Dexamethasone has many actions which include inducing the activity of certain metabolising enzymes of the liver. In particular, dexamethasone induces cytochrome P450 activity. Without being bound by theory, it is possible that metabolism of the ecteinascidin 743 by induced enzyme is giving rise to one or more metabolites which might be responsible for the enhanced effectiveness of the treatment with ecteinascidin 743.

Accordingly, we further provide:

combinations of ecteinascidins, notably ecteinascidin 743, with drugs inducing metabolic enzymes and in particular, cytochrome p450 enzymes;

EXAMPLES

The present invention is illustrated by the following two abstracts.

Ecteinascidin-743 (ET-743) in heavily pretreated refractory sarcomas : early results of the French experience.

Delaloge S, Misset J.L, Taamma A, Di Palma M, Guzman C, Brain E, Cottu P, Riofrio M, Jimeno J.M, Cvitkovic E.
Hop Paul Brousse, Centre René Huguenin, Hop Saint Louis, France. Pharma Mar, Très Cantos, Spain..

ET-743 is a new minor groove DNA binding agent of marine origin, currently in early phase II development. During the phase I trial testing the 24 hours continuous infusion given every 3 weeks the maximal tolerated dose was 1800 $\mu g/m^2$ and the recommended dose was 1500 $\mu g/m^2$. The limiting toxicities were neutropenia and thrombopenia. Fatigue and reversible transaminitis were also frequent. We report our current experience in treatment of refractory advanced sarcoma patients.
Patients characteristics : Twenty four patients received ET-743, 23 at recommended dose and schedule and 1 at the maximum tolerated dose. Nine of them were treated in the phase I study, 9 in an early phase II and 6 received this treatment in a compassionate use basis. Sex: 14 women/10 men; median age 46 (16-71); histology: leiomyosarcoma 6, liposarcoma 6, fibrosarcoma 4, angiosarcoma 1, rhabdomyosarcoma 1, osteosarcoma 2, other types 4; median number of previous chemotherapy regimens 2 (1-4), (all patients previously treated with anthracycline and alkylators); median PS 1 (0-2); median number of metastatic sites 1 (1-3). Toxicity is evaluable for 84 given cycles. Median number of cycles/ patient 3 (1-8). Grade 3-4 (NCI-CTC) toxicities are acute reversible transaminitis (46%), neutropenia (34%), thrombopenia (6%) nausea/vomiting (9%). Febrile neutropenia occurred in 2 cycles (2%). Grade 1-2 asthenia were observed in 42% of cycles. Antitumour activity 21 patients evaluable (3 patients too early for evaluation). Four PR (19%) (3.5, 6+, 6+, 6+ months), 3 MR (2+, 3+, 4+) and 7 disease stabilization (3 ongoing) were observed. Both osteosarcoma patients achieved a PR, the other two PR were observed in liposarcoma and fibrosarcoma. Median time to progression for the overall cohort is 10 weeks (range : 2-25). ET-743 is a promising agent with a Phase II program in patients with pretreated soft tissue sarcomas actively accruing.

Official Abstract Form

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Exploratory evaluation of the potential predictors for dose-limiting toxicities (DLTs) in patients treated with Ecteinascidin-743 (ET-743) as a 24-h intravenous (iv) infusion every 3 weeks and its relationship to pharmacokinetics (PK)

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We evaluated the potential predictors of ET-743 DLTs and its relationship to PK. Evaluation was performed with data from the 24 h iv infusion q 3 weeks Phase I study. DLT was defined as any grade ≥ 3 non-hematological toxicity (excluding reversible transaminitis, alopecia and emesis), grade 4 neutropenia longer than 5 days, febrile (>38° C) neutropenia or grade 4 thrombopenia. Two analysis were performed, one without PK including all 105 treatment courses, and other including PK parameters of the 2 initial courses. In both cases, 3 dose levels (34pts) were considered; 1200 (5pts), 1500 (25pts) (RD) and 1800 mcg/m2 (4pts) (MTD). The considered PK parameters were terminal half-life (t1/2), clearance (Cl), area under the curve (AUC) and volume of distribution (Vd) calculated by non-compartmental methods. Pts characteristics were: sex (14/20; M/F), age (median 59 yrs, range:19-75). Other potential predictors were: previous treatment (more than 2/1-2 previous lines), liver metastases (yes/no), bone metastases (yes/no), cycle number, dose, and baseline performance status, prothrombin time, partial thromboplastin time, albumin, bilirubin, alkaline phosphatase (AP), AST and ALT. For the initial univariate analysis Fisher's exact test for dichotomous variables, Mann-Whitney test for ordinal variables and Student's t-test for continuous variables were used. Variables with a p value < 0.20 were entered in a backward stepwise logistic regression model.

All observed DLTs (16 cycles/13 pts) were neutro- (9 cycles/7 pts) or thrombopenia (7 cycles/6 pts) related. The DLT likelihood increased with dose (p=0.012) and baseline AP (p=0.0026). 62 (34 1st/28 2nd) treatment courses given to 34 pts were included in the analysis including PK. DLT risk correlated with increasing baseline AP (p=0.081), and number of cycles given (p=0.052). Moreover, it correlated with PK features: increased AUC (p=0.044) and decreased Cl and Vd (p=0.047 and 0.043 respectively) in the multivariate analysis.

Increased baseline AP is a potential prospective predictor of ET-743 induced DLTs, but its value should be validated in further studies. The risk of DLT is higher on cycle 2 than in cycle 1. Increased AUC increases the risk of DLTs and both low Cl and low Vd are independent predictors of DLT.

Abstract classification

(Please check the most appropriate box)

- O Agents with unknown/uncertain targets
- O Animal models for drug evaluation
- O Antiangiogenic/antivascular agents
- O Antisense strategies
- O Apoptosis
- O Biological response modifiers and cytokines
- O Cancer vaccines/cellular therapy
- O Cell cycle regulators
- O Chemistry: combinatorial and innovative
- O Chemoprevention clinical studies
- O Chemoprevention targets (and biomarkers)
- O Clinical trial methodology (cytostatistics, surrogate endpoints)
- O Combinatorial approaches
- O Cyclins and CDK targets
- O Differentiation
- O DNA Repair
- O DNA-interactive agents
- O Drug delivery and prodrugs
- O Drug design
- O Drug resistance/modifiers
- O Drug transporters
- O Enzyme inhibitors (e.g., DHFR, Topo1/Topo2)
- O Formulation research
- O Gene therapy vector design
- O Genomics for target discovery (arrays and chips)
- O Growth factors and their receptors (including antihormonal)
- O Imaging approaches to drug evaluation
- O Immunological targets (tumor antigens, dendritic cells)
- O *In vitro* evaluation systems
- O Kinase inhibitors
- ✓ Marine compounds and other natural products
- O Mathematical modeling of drug design/drug action
- O Metastasis and invasion targets (e.g., MMP inhibitors, adhesion)
- O Methylation
- O Monoclonal antibodies and conjugates
- O New extracellular drug targets
- O New intracellular drug targets
- O Nutritional targets
- O Oncogene targets
- O Pharmacogenetics and drug metabolism
- ✓ Phase I studies - general
- O Phase I studies with molecular endpoints
- O Phase II studies - general
- O Phase II studies with molecular endpoints
- O Phosphokinase targets
- O Preclinical pharmacokinetics/ pharmacodynamics
- O Radiation interactive agents
- O Signal transduction/signaling targets
- O Structure-based drug design
- O Supportive care agents
- O Targets in medically underserved populations
- O Telomeres and chromosomal instability
- O Toxicity modulators
- O Toxicology
- O Tubulin-interacting agents
- O Other

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